

## Synthetic approaches to isocarbacyclin and analogues as potential neuroprotective agents against ischemic stroke

By: Ghina'a I. Abu Deiab, [Mitchell P. Croatt](#)

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### Abstract:

Isocarbacyclin is a valuable synthetic analogue of prostacyclin with potential neuroprotective effects for the treatment of ischemic stroke. Herein, we describe the synthesis of isocarbacyclin and bicyclic analogues in only 7–10 steps, with the  $\omega$ -side chain diversified at a late stage. A combination of new reaction design, function-oriented synthesis, and late-stage diversification led to a series of compounds that were tested for their neuroprotective activities. Efforts toward the synthesis of tricyclic analogues of isocarbacyclin, using the same combination of metal-catalyzed reactions, is also described.



**Keywords:** Isocarbacyclin | Synthesis | Analogues | Neuroprotective | Stroke

### Article:

#### 1. Introduction

The last century has experienced the development of many synthetic strategies and syntheses of medicinal leads.<sup>1</sup> Total syntheses of complex small molecules, including natural products and synthetic variants, exhibit almost infinite variations as they can afford unique approaches and disconnections. Each target presents a puzzle that requires scientists to solve challenges to their structures for which solutions may not be available using known synthetic methods. Thus, the design and development of new reactions has a powerful influence on the pathways that can be imagined to construct molecules.

One of the challenges in total synthesis is the number of steps required to synthesize a target molecule. Increasing the number of steps has a negative influence on the required time, cost and waste.<sup>2, 3</sup> Improvements in the step-economy of a synthetic plan is possible by utilization of a few key strategies: 1) new reaction design; 2) function-oriented synthesis; 3) semi-synthesis; and 4) late-stage diversification.<sup>2, 3, 4</sup> The first three strategies shorten the number of steps to a single compound, and the last method shortens the total number of steps to more than one compound by judiciously choosing a diversification point that has the highest molecular complexity while still allowing for the desired modifications. As will be illustrated herein, these different strategies are not mutually exclusive so more than one of these can be used to greatly shorten the total number of steps in a synthetic project.

Isocarbacyclin, first synthesized in the 1980's,<sup>5</sup> is a stable synthetic analogue of prostacyclin (1, Fig. 1).<sup>6</sup> Prostacyclin (1) is a highly potent vasodilator and inhibitor of platelet aggregation, however; it is inherently unstable due to the vinyl ether moiety in its structure. This instability limits its use in clinical applications.<sup>7, 8, 9, 10</sup> Isocarbacyclin (2) and clinprost (3) were developed and found to be more stable than prostacyclin (1, Fig. 1).<sup>6, 11, 12, 13</sup>

In addition to vasodilation, both isocarbacyclin (2) and clinprost (3) were reported to be highly potent neuroprotective agents for the treatment of ischemic stroke.<sup>11, 13-17</sup> Stroke is one of the leading causes of death and has been known to cause serious injuries to many people.<sup>18</sup> Between the two types of stroke, hemorrhagic and ischemic, ischemic stroke accounts for the majority of incidents with about 87% of strokes being ischemic.<sup>19, 20</sup> Despite decades of research, treatment options for ischemic stroke remain limited. Currently the only FDA-approved therapy is tissue-plasminogen activator (tPA), which has a limited time window.<sup>17, 21, 22</sup> Other medicines that are available in the market are only used as preventative therapies for protection against platelet aggregation, such as clopidogrel or against blood clotting such as warfarin.<sup>23</sup> Therefore, the search for novel therapeutics that have the potential to protect brain tissue from this damage is urgent.<sup>21, 24</sup>

Isocarbacyclin (2) and clinprost (3) are promising neuroprotective agents, however, exploration of their biological activity has been limited as a result of the length of their syntheses. Both molecules were synthesized by several groups with diverse approaches, however, most were 20 or more steps with the shortest reported syntheses requiring 15 steps.<sup>25-37</sup> Isocarbacyclin (2) possesses a bicyclo[3.3.0]octene system with four contiguous stereocenters and two side chains; an octenol  $\omega$ -side chain and an  $\alpha$ -side chain that contains the pentanoic acid connected to the endocyclic alkene.<sup>4</sup> Synthetic challenges, including the construction of the bicyclic ring system and regioselectivity of both the endocyclic double bond (C6-C9 $\alpha$ ) and the  $\alpha$ -sidechain, are some of the difficulties that must be surmounted in the synthetic approaches.<sup>38, 39</sup> Moreover, there is the problem of how to stereoselectively introduce the four contiguous stereocenters. With respect to examining analogues, it is valuable to explore variability with the  $\omega$ -sidechain since this region of the molecule has been shown to impact activity.<sup>39</sup>



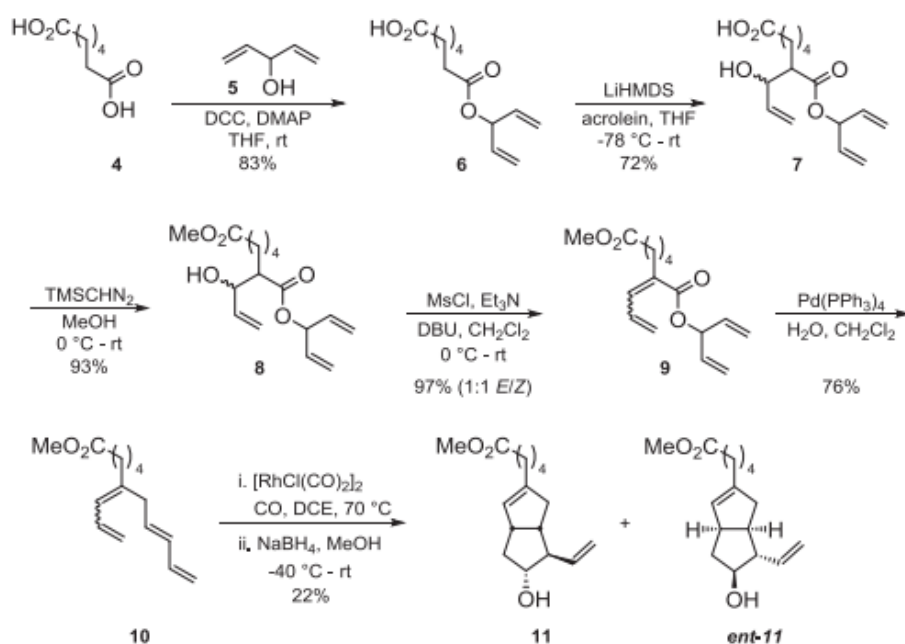
Fig. 1. Prostacyclin (1), isocarbacyclin (2) and clinprost (3) structures

Croatt et al. reported the synthesis of clinprost (3) in only 9 total steps utilizing inexpensive and commercially available starting materials.<sup>4, 40</sup> This synthetic route was used, with several optimizations presented herein, to synthesize isocarbacyclin (2) and new bicyclic analogues in which the  $\omega$ -side chain was diversified at a late stage in the synthesis using different alkenes. Moreover, efforts toward the synthesis of tricyclic analogues will be described herein by a different synthetic approach using the same metal-catalyzed key reactions used in the synthesis of isocarbacyclin.

## 2. Results and discussion

### 2.1 Synthesis of isocarbacyclin and its bicyclic analogues

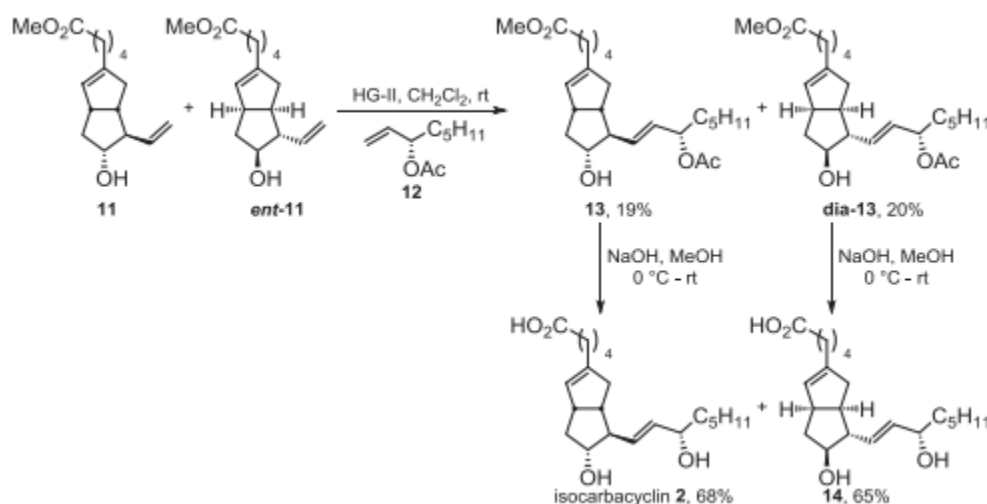
The step-economical synthesis of clinprost (3) reported by the Croatt Group was further optimized to make isocarbacyclin's bicyclic building block (11, Scheme 1), which was made in only 6 steps from commercially available materials.<sup>40</sup> This route was designed to enable late-stage diversification by using a cross-metathesis reaction of different commercially available alkenes to afford isocarbacyclin and different analogues. The synthesis of the core begins by reacting excess pimelic acid (4) with bis-allylic alcohol (5) to generate monoester 6 as a major product, followed by an aldol condensation with acrolein. A limitation of the second step was the quick polymerization of acrolein during the reaction workup and purification. Acidic workup was highly beneficial for enabling solvation of the acrolein polymers. Various conditions were screened to find that using LiHMDS as a base in THF gave yields that ranged widely, from 53% to less than 15%. Later, we found that using solid LiHMDS increased the yield up to 72% with good reproducibility. Another important aspect of this reaction was the addition of the lithium enolate to a solution of acrolein, instead of adding acrolein to the enolate.



Scheme 1. Synthesis of the bicyclic building block (11)

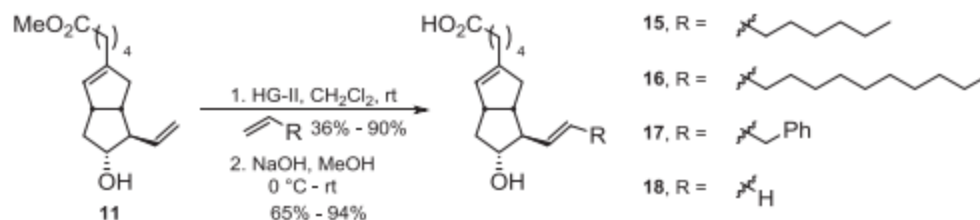
The resulting acid (7) was subjected to methylation and dehydration to generate ester 9 in a 1:1 ratio of E:Z isomers, which was reacted with Pd<sup>0</sup> to accomplish an allylic rearrangement and decarboxylation to form tetraene 10. This new type of decarboxylation has been studied in more detail by the Croatt Group.<sup>41</sup> Tetraene (10) is then reacted with a RhI catalyst under an atmosphere of carbon monoxide in a bis-diene [2 + 2 + 1] cycloaddition reaction followed by an in situ reduction. The four stereocenters of bicycle 11 are installed with the same relative configuration as in isocarbacyclin (2). The yield is low as only the Z-isomer reacts to give bicycle 11 while the E-isomer remains unchanged. Moreover, the intermediate ketone isomerizes over time or under more forcing conditions to the more stable and undesired isomer (Scheme S1, Supplementary Material). Different conditions were screened in order to more efficiently form the desired product, and the optimal conditions were found to run the reaction for 8–10 h at 70 °C (22% yield over 2 steps; Table S1, Supplementary Material). The yield for this step led us to design a route for a different type of analogues, tricyclic, where the double bond in the tetraene derivative is locked in the Z-form only, vide infra.

To complete the synthesis of isocarbacyclin (2), a Ru<sup>II</sup>-catalyzed cross-metathesis reaction was utilized to attach the ω-side chain. The parent side chain, (S)-3-acetoxy-oct-1-ene (12), was synthesized using an enzymatic resolution of racemic 1-octen-3-ol.<sup>42</sup> The cross-metathesis reaction yielded a mixture of enantiomerically enriched diastereomers since the bicyclic core was racemic and the side chain was enantioenriched. The diastereomeric mixture of 13 and dia-13 was separated using standard silica gel chromatography. Hydrolysis of the methyl ester and acetate protecting group using NaOH generates isocarbacyclin (2) and its diastereomer (14), each in an enantioselective fashion (Scheme 2).



Scheme 2. Enantioselective synthesis of isocarbacyclin (2) and its diastereomer (14).

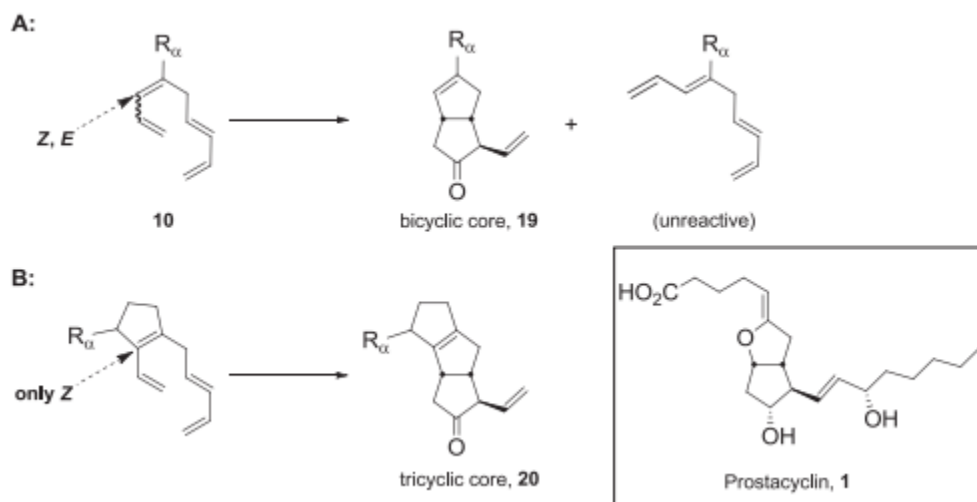
With the completed bicyclic core (11) in hand, a cross-metathesis approach to analogues was utilized using three different available terminal alkenes, followed by hydrolysis of the methyl ester (Scheme 3). Additionally, the bicyclic core without a side chain (11) was directly subjected to hydrolysis. Cross-metathesis reactions with p-styrene and myrcene were attempted, but only homocoupling byproducts were observed.



Scheme 3. Successful synthesis of analogues of isocarbacyclin.

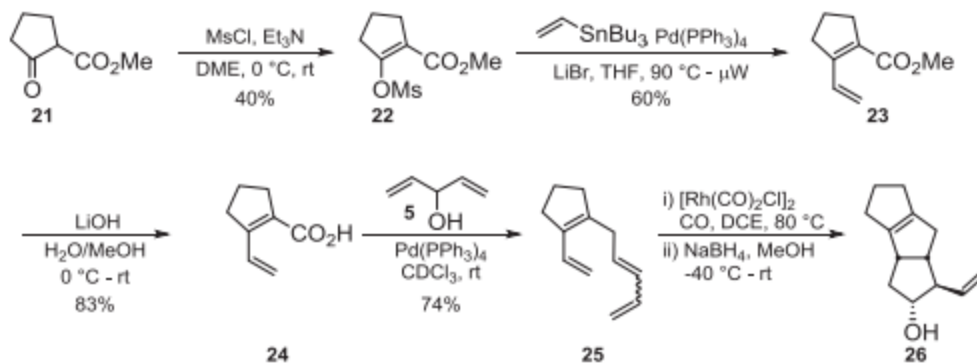
## 2.2 Efforts toward the synthesis of tricyclic isocarbacyclin analogues

During the synthesis of isocarbacyclin (2) and its analogues, one focus was on optimizing the bis-diene [2 + 2 + 1] cycloaddition of tetraene 10 that yielded the bicyclic building block (19) for future analogues. We were able to increase the yield to 22%, but were not able to improve the yield further due to limitations related to the E-isomer being unreactive (Scheme 4A). This issue led us to design a new analogue whereby the bis-diene is locked as the Z-isomer to generate a tricyclic core (20) for new types of isocarbacyclin analogues (Scheme 4B). Importantly, the tricyclic analogues position the  $\alpha$ -side chain in a manner similar to prostacyclin (1). Further validation of this type of analogue is the fact that prostacyclin has tricyclic analogues that are currently in clinical use as vasodilators including beraprost and treprostinil.<sup>43</sup>



Scheme 4. Bicyclic (19) versus tricyclic (20) building blocks.

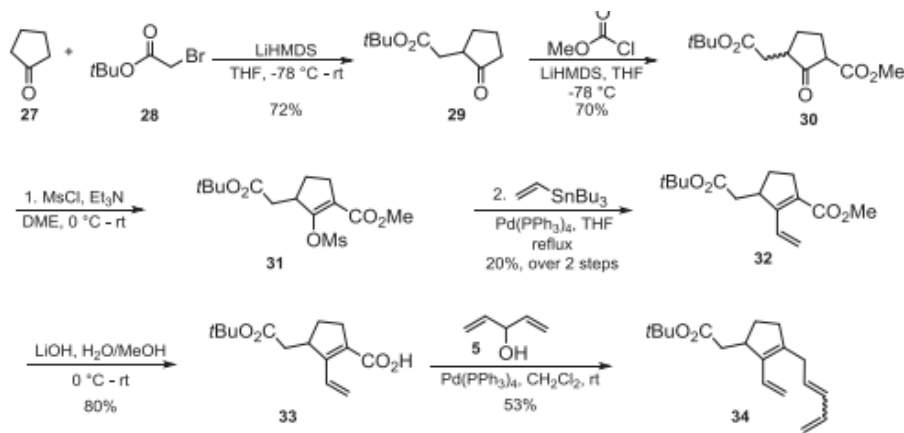
A model system for the tricyclic analogues was first developed to test if the Pd-catalyzed decarboxylation and Rh-catalyzed cycloaddition reactions would be successful (Scheme 5). The model system synthesis starts from commercially available  $\beta$ -ketoester 21 that is converted to mesylate 22 using MsCl and Et<sub>3</sub>N. Mesylate 22 was found to be unstable and taken directly to the Stille coupling without further purification to afford dienolic ester 23.



Scheme 5. Synthesis of the tricyclic core (26) in the model system.

Different conditions were screened to optimize the Stille coupling reaction (Table S2, Supplementary Material), to find that running the reaction at 90 °C in a microwave produces a 60% yield. The resulting ester (23) from the Stille coupling was then subjected to hydrolysis with LiOH to afford dienoic acid 24. Although a one-flask reaction for Stille coupling and hydrolysis was successful to yield dienoic acid 24, sufficient purification of this compound was problematic due to streaking of the stannane byproducts. Gratifyingly, dienoic acid 24 underwent an intermolecular decarboxylative coupling with bis-allylic alcohol (5) when subjected to Pd<sup>0</sup> conditions. The decarboxylated product (25) was subjected to Rh<sup>I</sup> catalysis under a carbon monoxide atmosphere with several conditions to yield traces of tricycle 26 (Table S3, Supplementary Material). Tricycle 26 was not fully characterized due to the volatility of the starting material and the isomerization of the product, however, it was clear that both reactions, decarboxylation and cycloaddition, were successful which validated moving from the model system to the actual synthetic route of the tricyclic analogue.

Based on the results of the model system, a similar synthetic scheme for the tricyclic core (20) was developed, starting with cyclopentanone (27). Reaction with *t*-butyl bromoacetate (28) produced ketone 29 (Scheme 6), which was then reacted with methyl chloroformate, using LiHMDS as a base, to provide diester 30. It was found that allowing the methylcarboxylation reaction to warm to room temperature for more than four hours resulted in significant decomposition. As a result, the reaction was left in the cooling bath for four hours to optimally synthesize the diester (30).

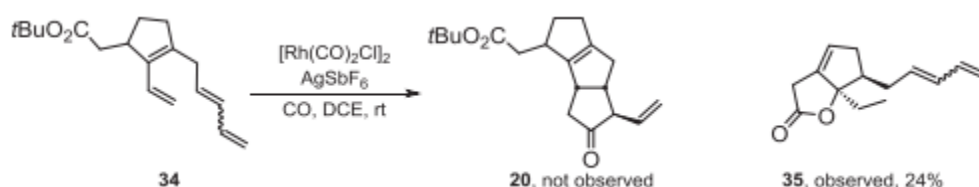


Scheme 6. Synthesis of tetraene building block (34) for the tricyclic isocarbacyclin analogue.



Diester 30 was expected to act similarly in the mesylation as in the model system. Unfortunately, an unknown byproduct formed in addition to the desired mesylate (31) when similar conditions were used. Different conditions were screened to form the mesylate, bromide or triflate derivatives (Table S4, Supplementary Material), but all trials either resulted in a byproduct along with the product in the case of the mesylate and the bromide or no reaction in the case of the triflate. Although not ideal, the unoptimized crude mesylate product was successfully subjected to Pd<sup>0</sup> catalysis for the Stille coupling to generate dienoic ester 32 in a 20% yield over the two steps. Dienoic ester 32 underwent chemoselective hydrolysis of the methyl ester to afford dienoic acid 33. The intermolecular decarboxylative coupling reaction with divinylcarbinol was again successful, which yielded the requisite tetraene 34 to generate tricyclic isocarbacyclin analogues.

Tetraene 34 was expected to react in the bis-diene [2 + 2 + 1] reaction similar to the model system and isocarbacyclin synthesis. However, it did not react when subjected to [RhCl(CO)<sub>2</sub>]<sub>2</sub> under carbon monoxide atmosphere at 80 °C. Using more forcing conditions by the addition of AgSbF<sub>6</sub> to generate a cationic rhodium catalyst, a cyclization reaction occurred with the pendant ester to generate lactone 35 (Scheme 7). Under a variety of solvents, catalysts, temperatures, and additives, tricycle 20 was never observed. The mechanism for the process to form lactone is still under investigation but the lack of formation of tricycle 20 requires a reanalysis of the synthetic approach.



Scheme 7. Cyclization of bis-diene 34 to afford bicycle 35.

### 2.3. Biological evaluation of isocarbacyclin and its bicyclic analogues

Isocarbacyclin and bicyclic analogues (2, 15–18) were tested *in vitro* for neuroprotection using embryonic mouse cortical neurons. The use of primary cultures more closely approximate normal neurons than is possible using cell lines. It has previously been shown that isocarbacyclin derivatives bind to and protect certain areas of the brain, with the cortex being one of the areas protected under ischemic conditions.<sup>44</sup> Two separate assays were run, one examining neuroprotection from glucose deprivation, and a second one where the cells were deprived of both glucose and oxygen. The second condition is a more severe stress, which more closely mimics ischemia and reperfusion. Unfortunately, the compounds showed neuronal cell toxicity in the assays with minimal, if any, neuroprotection observed.

## 3. Conclusion

The enantioselective total synthesis of isocarbacyclin was described herein using only 9 steps from inexpensive and commercially available materials. Three metal-catalyzed reactions, including Pd<sup>0</sup>-catalyzed decarboxylation, Rh<sup>I</sup>-catalyzed cycloaddition and Ru<sup>II</sup>-catalyzed cross metathesis reactions, were utilized in this synthesis. Other analogues were synthesized by attaching different ω-side chains in a late-stage to shorten the synthesis to 7–10 steps. Another

generation of isocarbacyclin analogues was developed to increase the yield of the cycloaddition step compared to isocarbacyclin synthesis and to mimic the structure of the endogenous analogue prostacyclin. A model system worked successfully for the Pd<sup>0</sup>-catalyzed decarboxylation and Rh<sup>I</sup>-catalyzed bis-diene [2 + 2 + 1] cycloaddition reactions that were used in the synthesis of isocarbacyclin. However, ester substitution of the cyclopentane ring resulted in an unexpected lactonization reaction. For future analogues of this type, the carboxyl group will be revealed at a late stage in the synthesis. Isocarbacyclin and its bicyclic analogues were tested in vitro against ischemic stroke, and a detrimental level of toxicity was observed.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.bmc.2018.12.010>.

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